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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,779	06/29/2005	Kevin L. Rozwadowski	4810-69922-01	5541

24197 7590 06/02/2006

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EXAMINER
LIETO, LOUIS D

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/516,779	ROZWADOWSKI ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *2 and 5-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction requirement was received on 4/05/2006. Claims 1-23 are pending in the instant application. Applicant's election with traverse of Group II, claims 1,3,4,22,23, drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of a host, wherein the host is capable of expressing the RT at the same time as, or after, transforming the host, and a gene targeting construct., is acknowledged.

Claims 2 and 5-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/28/2006.

Response to Arguments

Applicant's election with traverse of Group II in the reply filed on 4/05/2006 is acknowledged. Applicant argues that the inventions share a special technical feature. However, as was previously determined in the International Preliminary Examination Report, the claims lack novelty and/or an inventive step over the prior art. Further as previously stated:

Inventions I-VI lack a unifying special technical feature. Applicant provided reference of Mao et al. describes the expression of ssDNAs by retrons in eukaryotic cells to form triple helices has been described in the prior art (Mao et al. (1995) JBC 270:19684-19687; p. 19687, last paragraph - p. 19688, first paragraph). Further, applicant provided reference of Datta et al. describes the successful use of a triple helix forming SSDNA as a gene-targeting agent (Datta et al. (2001) Nucleic Acids Research 29:5140-5147; p. 51.44, last paragraph- p. 5145, first paragraph). Therefore, it would have been obvious to the ordinary practitioner in the art at the time of the instant invention to modify a target locus with a gene-targeting construct in view of the teachings of Mao et al. and Datta et al. The cited prior art provides the requisite teaching, suggestion and motivation to make and use the claimed invention.

Since the claimed subject matter was known from the prior art documents of Mao et al. and Datta et al., the subject matters of claims 1-23 are not so linked as to form a single general

inventive concept (Rule 13.1 PCT) as they appear not to be linked by a new and inventive common special technical feature in the sense of Rule 13.2 PCT by taking into account the state of the art.

The unity of applicant's invention was broken by the prior art of Mao et al. and Datta et al. because the special technical feature of modifying a nucleic acid target locus with a retron was known in the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1,3,4,22, and 23 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,3,4,22, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modifying a target nucleic acid of interest at a target locus within a genome of a host, *in vitro,* comprising:

a) introducing into the host cell, *in vitro,* by transformation with a DNA comprising a nucleic acid sequence encoding a reverse transcriptase (RT) and a gene targeting construct (GTC) and culturing the host so as to:

i) express an mRNA from the GTC, wherein the mRNA is capable of self-priming reverse transcription by the RT

ii) wherein at least a portion of the gene-targeting message RNA is reverse transcribed to produce a gene targeting substrate (GTS) having a gene targeting

nucleotide sequence (GTNS), wherein the GTNS is homologous to the target

locus and comprises a sequence modification compared to the target nucleic acid

iii) wherein the GTNS inserts, deletes or substitutes one or more bases of the sequence of the

target nucleic acid;

and,

b) selecting a host cell having the GTNS mediated sequence modification at the target locus,

does not reasonably provide enablement for a method of modifying a target nucleic acid of

interest at a target locus within a genome of a host comprising:

a) introducing into the host any gene targeting construct (GTC) by any means and culturing the

host so as to:

i) express the gene-targeting construct encoding a gene-targeting message

RNA, to produce the gene targeting message RNA capable of self-priming reverse

transcription by a reverse transcriptase (RT);

ii) reverse transcribe at least a portion of the gene targeting message RNA

to produce an *in vivo* gene targeting substrate (GTS) having a gene targeting

nucleotide sequence (GTNS), wherein the GTNS is homologous to the target

locus and comprises a sequence modification compared to the target nucleic acid;

and,

b) selecting a host having the sequence modification at the target locus. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of any host comprising:

a) introducing into any host any gene targeting construct (GTC) by any means and culturing the host so as to:

i) express the gene-targeting construct encoding a gene-targeting message RNA, to produce the gene targeting message RNA capable of self-priming reverse transcription by a reverse transcriptase (RT);

ii) reverse transcribe at least a portion of the gene targeting message RNA to produce an *in vivo* gene targeting substrate (GTS) having a gene targeting nucleotide sequence (GTNS), wherein the GTNS is homologous to the target locus and comprises a sequence modification compared to the target nucleic acid;

and,

b) selecting a host having the sequence modification at the target locus. Wherein the GTC is any nucleic acid (RNA or DNA) and is introduced into the host by any method, such as transformation, cross breeding or cell fusion. Wherein the RT is administered at the same time as or after the gene-targeting construct. The language of claim 1 is quite broad, however has been interpreted to limit the method to *in vitro* modification since the host must be cultured after introduction of the GTC.

The specification does not provide any guidance on how to express an mRNA from any GTC other than a GTC that consists of DNA. Further the art teaches that mRNA can only expressed from DNA. Therefore the skilled artisan would be unable predict how to practice the claimed invention using a GTC consisting of any other nucleic acid sequence other than DNA.

Further, the specification does not provide any guidance on the integration of the GTC into the host's genome, or the maintenance of the GTC in the nucleus or cytoplasm throughout mitotic or meiotic divisions. Specifically there is no guidance that the GTC contains an origin of replication or any other structural features that would allow it to independently segregate with the host's chromosomes during cell division. Without such guidance the ordinary practitioner in the art would not be able to predict how to reliably introduce the GTC into a non-GTC carrier host by crossbreeding or cell fusion. In part this is due to the complete lack of guidance in the specification that a GTC integrated into the host genome is capable of producing an mRNA at sufficient levels to be reversed transcribed into a GTS with a GTNS. Further, the specification does not provide any guidance on how to cross breed a cultured host. It is noted that the working examples only disclose using a yeast eukaryote host with the claimed method (Examples 1-12). Further, the specification does not provide any guidance on modifying a host to express the RT after the host is transformed with the GTC. There is no information provided in the specification that would allow the artisan to predict how long an interval between transforming the host with a GTC and modifying said host to express the GT could be tolerated an still successfully practice the claimed method. This is due to the lack of guidance in the specification on the stability or half-life of the GTC. Additionally, the claims encompass any sequence modification to the target locus, such modification could encompass DNA methylation or other non-sequence specific modifications. However, the specification does not provide any guidance on how to methylate a target nucleic acid using the claimed method.

There is no guidance provided in the specification on delivery of the GTC to a multi-cellular host, which can be cultured. Further, the specification does not provide guidance on the

transfer of a GTC to a multi-cellular host so as to overcome the problems associated with gene therapy. Verma et al. states that in the past, the Achilles heel of gene therapy was gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. These issues remain as current problems in the field of gene therapy. Pfeifer and Verma state that even "though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge {Pfeifer and Verma (2001) Annu. Rev. Genomics. Hum. Genet. 2:177-211; pg. 177, pgph 1}. Johnson-Saliba et al. concurs stating, "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery." {Johnson-Saliba et al. (2001) Curr. Drug. Targets 2:371-99; Abstract}. Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based-medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non-toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorgenicity." {Shoji et al. (2004) Current Pharmaceutical Design 10 :785-796}.

Given the lack of guidance in the specification on how to practice the method in a manner commensurate in scope with the claims, an ordinary practitioner in the art would be unable to predict how to practice the claimed method, except as a method of modifying a target nucleic acid of interest at a target locus within a genome of a host, *in vitro,* comprising:

a) introducing into the host cell, *in vitro,* by transformation with a DNA comprising a nucleic acid sequence encoding a reverse transcriptase (RT) and a gene targeting construct (GTC) and culturing the host so as to:

i) express an mRNA from the GTC, wherein the mRNA is capable of self-priming reverse transcription by the RT

ii) wherein at least a portion of the gene-targeting message RNA is reverse transcribed to produce a gene targeting substrate (GTS) having a gene targeting nucleotide sequence (GTNS), wherein the GTNS is homologous to the target locus and comprises a sequence modification compared to the target nucleic acid

iii) wherein the GTNS inserts, deletes or substitutes one or more bases of the sequence of the target nucleic acid;

and,

b) selecting a host cell having the GTNS mediated sequence modification at the target locus, without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,3,4,22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of a host comprising: introducing into the host a gene targeting construct

and culturing the host. This has been interpreted to limit the claim to *in vitro* embodiments where the host is culture. Claim 4 depends from claim 1 and limits the GTC to an embodiment wherein the GTC is introduced by crossbreeding. However, it is unclear from the specification how cultured hosts are to be crossbred. Therefore the metes and bounds of claim 4 cannot be determined.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: failure to provide for a step between the reverse transcription of the mRNA to make the GTS and selecting a host having a sequence modification. The claim omits the essential step wherein the GTS mutates the target nucleic acid sequence in the host genome. Claims 3,4,22 and 23 depend from claim 1.

Claims 22 and 23 are rejected because they are improperly dependent from claim 1. Claim 1 is drawn to a method. Claims 22 and 23 are limited to a construct. Therefore the metes and bounds of claims 22 and 23 cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,3,4,22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0082800 A1 (5.01.2003) priority to (10.09.1998), hereafter referred to as Conrad et al.

Conrad et al. provides guidance on an expression vector for altering expression of a target nucleic acid sequence in a host cell by production of single-stranded cDNA (ssDNA) in the host cell in vivo. The expression vector is comprised of a cassette comprising a sequence of interest, an inverted tandem repeat, and a primer binding site 3' to the inverted tandem repeat, and a reverse transcriptase coding gene, and may be transfected into the host cell in a method of sequence modification, such as site directed mutagenesis or gene therapy for therapeutic applications (Abstract; pgph 18). Transcription of the cassette by the host cell produces an RNA template that is reverse transcribed with the product of the RT coding gene to produce ssDNA of a specified sequence. The resulting ssDNA binds to an endogenous target nucleic acid sequence (Abstract). Wherein, hosts that have a sequence modification at the target locus can be selected for (pgph 93). The cassette may be introduced into the host by transformation (pgph 22,45). Wherein the ssDNA may contain any practical size sequence of interest as an insert, such as 31 bp, 1.2 kb, 2.4 kb in length (Fig. 4A,4b, pgph 99, 108-117). It is inherent that an insert used for site directed mutagenesis will have at least one bp that is different from the target nucleic acid sequence. Therefore in sequences less than 100 bp long this will provide for 99% or lower sequence similarity. Thus, by teaching all the limitations of the claims as written, Conrad et al. anticipates the instant invention as claimed.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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